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Palladium-catalyzed regio- and enantio-selective allylic substitution reaction of monosubstituted allyl substrates with benzyl alcohols

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This paper is dedicated to Professor H. B. Kagan on the occasion of his 80th birthday

ABSTRACT

Regio- and enantio-selectivities in Pd-catalyzed allylic substitution reaction of monosubstituted allylic substrates with substituted benzyl alcohols were realized, affording the corresponding products in high regioselectivity (up to 93/7) and enantioselectivity (up to 96%).

1. Introduction

Transition metal-catalyzed enantioselective allylic substitution reaction has a long history over 30 years, and has become a very powerful tool for construction of carbon–carbon and carbon–heteroatom bonds, providing important optically active materials.[1] Among the various nucleophiles used in such reaction, relatively hard oxygen nucleophiles received scarcely less attention,[2] in contrast to widely used carbon and nitrogen nucleophiles.[1] In the later part of last century the first Pd-catalyzed enantioselective allylic substitution of monosubstituted allylic substrate with phenols was reported by Trost et al.[3] Since then, examples of the reactions with *O*-nucleophiles using other metal-catalysts such as Ir,[4] Rh,[5] and Ru[6] appeared, and excellent selectivity was achieved. Very recently, Chan documented a Pd-catalyzed asymmetric allylic substitution of racemic 1,3-diphenyl-2-propenyl acetate with relatively hard aliphatic alcohols to generate chiral ethers with excellent enantioselectivities.[7] However, Pd-catalyzed regio- and enantio-selective allylic substitution of monosubstituted allylic substrate with alcohols is still unknown. Our group has focused on the regio-, diastereo-, and enantio-selectivities in Pd-catalyzed allylic substitution reaction of monosubstituted allylic substrates with different nucleophiles.[8] Herein, we report a regio- and enantio-selective allylic substitution reaction of monosubstituted allylic substrate with substituted benzyl alcohols using Pd-catalyst with SiocPhox as a ligand.

2. Results and discussion

Initially, we examined the reaction of cinnamic alcohol acetate **1a** with benzyl alcohol **2a** in the presence of catalyst derived from $[PdC_3H_5Cl]_2$ (2 mol %) and SiocPhox (S_{phos}, *R*)-**L1** (4 mol %), using Cs_2CO_3 as a base at room temperature in toluene. Unfortunately, only cinnamic alcohol was obtained, due to hydrolysis of acetate under basic condition. To avoid the side reaction, more bulky *tert*-butyl cinnamyl carbonate **1b** instead of **1a** was tested, and the desired product **3** was provided in 82% yield with branched/linear ratio of 66/34 and 58% ee for branched one. These promising results promoted us to investigate the influence of the parameters on the reaction further (Table 1).

It can be seen that the ligand with different combination of chiral elements showed its great impact on the reaction (Table 1, entries 1–5). The ligands (*S*, S_{phos}, *S*)-**L2**, (*S*, S_{phos}, *R*)-**L4**, and (*S*, R_{phos}, *R*)-**L5** gave much lower selectivity compared to (*S*, R_{phos}, *S*)-**L3** (Table 1, entries 2, 4, and 5 vs entry 3). These results showed that the ligand (*S*, R_{phos}, *S*)-**L3** was the most effective one and demonstrated that the chiralities in **L3** were matched. With **L3** as a ligand, we investigated the solvent effects on this process (Table 1, entries 6–10). The reaction proceeded smoothly in DCM or Et_2O albeit with poor regio- and enantio-selectivity (Table 1, entries 6 and 9). The reaction became sluggish in THF or DME, providing trace amount of product (Table 1, entries 7 and 8). No reaction occurred in MeCN (Table 1, entry 10). However, toluene was identified as the optimal solvent in terms of both regio and enantioselectivities (Table 1, entry 3). To improve further the selectivity, we evaluated the influence of temperature on the reaction (Table 1, entries 11–14). When the temperature was down to −5 °C, the regio- and enantio-selectivities were improved greatly (Table 1, entry 11 vs entry 3). Both regio- and enantio-selectivities increased slightly at −15 °C, but the yield lowered from 82% to 66% (Table 1, entry 12 vs entry 11). When the temperature dropped further to −25 °C, the selectivity of the reaction decreased slightly, and chemical yield lowered to 30% (Table 1, entry 13 vs entry 12). At −5 °C, ligand **L6** with more bulky ^{t}Bu group on oxazoline was tested, the regioselectivity and enantioselectivity were improved slightly whereas with much lower chemical yield (Table 1, entry 14 vs entry 11).

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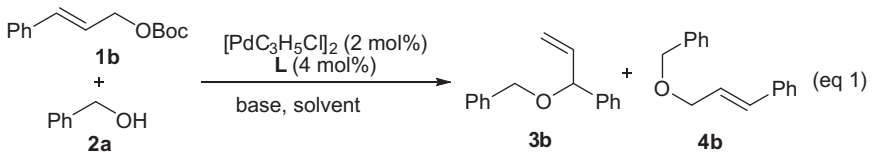
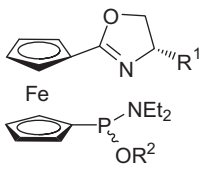
Table 1
Optimization of the reaction parameters[a]





R^1 = H (S_{phos}, R)-**L1**
R^1 = ^{i}Pr (S, S_{phos}, S)-**L2**
R^1 = ^{i}Pr (S, R_{phos}, S)-**L3**
R^1 = ^{i}Pr (S, S_{phos}, R)-**L4**
R^1 = ^{i}Pr (S, R_{phos}, R)-**L5**
R^1 = ^{t}Bu (S, R_{phos}, S)-**L6**

L2, **L3**, **L6**:
R^2 = (*S*)-2-(2'-hydroxy-1,1'-bi-naphthyl)

L1, **L4**, **L5**:
R^2 = (*R*)-2-(2'-hydroxy-1,1'-bi-naphthyl)

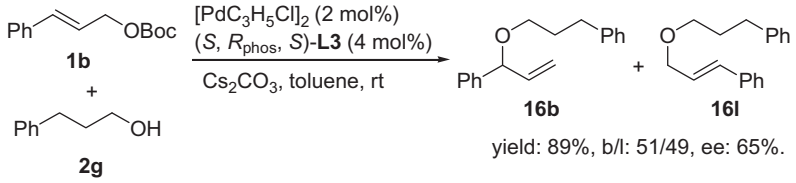
Entry	*T* (°C)	Solvent	Base	L	Yield[b] (%)	**3b**/**4b**[c]	ee[d] (%)
1	rt	Toluene	Cs_2CO_3	**L1**	82	66/34	58 (*R*)
2	rt	Toluene	Cs_2CO_3	**L2**	56	29/71	16 (*R*)
3	rt	Toluene	Cs_2CO_3	**L3**	80	70/30	85 (*R*)
4	rt	Toluene	Cs_2CO_3	**L4**	40	65/35	20 (*S*)
5	rt	Toluene	Cs_2CO_3	**L5**	80	56/44	63 (*R*)
6	rt	DCM	Cs_2CO_3	**L3**	87	50/50	63
7	rt	THF	Cs_2CO_3	**L3**	Trace	—	—
8	rt	DME	Cs_2CO_3	**L3**	Trace	—	—
9	rt	Et_2O	Cs_2CO_3	**L3**	71	50/50	60
10	rt	MeCN	Cs_2CO_3	**L3**	nr[e]	—	—
11	−5	Toluene	Cs_2CO_3	**L3**	82	90/10	96
12	−15	Toluene	Cs_2CO_3	**L3**	66	92/8	97
13	−25	Toluene	Cs_2CO_3	**L3**	30	87/13	94
14	−5	Toluene	Cs_2CO_3	**L6**	64	91/9	98
15	−5	Toluene	None	**L3**	nr[e]	—	—
16	−5	Toluene	*n*-BuLi	**L3**	75	0/100	—
17	−5	Toluene	CsF	**L3**	30	56/44	nd[e]

[a] Molar ratio: **2a**/**1b**/Cs_2CO_3/$[PdC_3H_5Cl]_2$/**L** = 3/1/3/0.02/0.04.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] nr = no reaction; nd = not determined.

We also investigate the influence of base on the reaction at −5 °C. Base is necessary for the reaction, because reaction did not take place in its absence (Table 1, entry 15). Only linear product was obtained employing *n*-BuLi as base, (Table 1, entry 16). In case of CsF as base, inferior results were provided in terms of yield and regioselectivity (Table 1, entry 17). Several other bases such as K_2CO_3, Na_2CO_3, $ZnEt_2$, and NEt_3 gave no product while NaH or KO-Bu^t as base made the reaction complex (not shown in table).

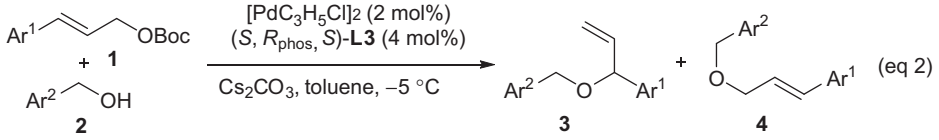
The substrate scope of the reaction was examined using the catalyst derived from $[PdC_3H_5Cl]_2$ and **L3** in the presence of Cs_2CO_3 as base in toluene (Table 2). A wide range of allyl carbonates **1** and substituted benzyl alcohols **2** were suitable for the Pd-catalyzed regio- and enantio-selective allylic substitution reaction, affording branched products with high regioselectivity and enantioselectivity (Table 2, entries 1–9).[9] The regioselectivity was sensitive to the substituent on allyl carbonates **1**. The reaction of *p*-$MeOC_6H_4$ substituted allylic carbonates **1d** afforded product with highest regioselectivity (Table 2, entry 3) while the incorporation of other aryl group or other substituents on phenyl ring on the allylic carbonates **1** led the slight decrease of regioselectivity (Table 2, entries 2 and 4–9 vs entries 1 and 3). Allyl carbonates **1** with 2-furyl, *p*-ClC_6H_4, or *p*-BrC_6H_4 as substituents showed low reactivity, providing corresponding branched products with moderated yield (Table 2, entries 5, 8, and 9). The substituted benzyl alcohols **2b**–**f**, with either electron-withdrawing groups or electron-donating groups provided the products with similar enantioselectivity but with a little bit lower yields (Table 2, entries 10–13). Introduction of the *p*-NO_2 group into benzyl alcohol retarded the reaction (Table 2, entry 14).

Primary aliphatic alcohol **2a**, which could not react with the allyl carbonates **1b** under the reaction conditions of Table 2, afforded



yield: 89%, b/l: 51/49, ee: 65%. (3)

Table 2
Pd-Catalyzed regio- and enantio-selective allylic substitution reaction of monosubstituted allylic carbonates **1** with substituted benzyl alcohols **2**[a]



Entry	**1**, Ar^1	**2**, Ar^2	Yield[b] (%)	**3**/**4**[c]	ee[d] (%)
1	**1b**, Ph	**2a**, Ph	82	90/10	96
2	**1c**, *p*-MeC_6H_4	**2a**, Ph	87	87/13	90
3	**1d**, *p*-$MeOC_6H_4$	**2a**, Ph	82	93/7	95
4	**1e**, 1-naphthyl	**2a**, Ph	93	88/12	93
5	**1f**, 2-furyl	**2a**, Ph	62 (85[e])	71/29	85
6	**1g**, *m*-$MeOC_6H_4$	**2a**, Ph	84	81/19	88
7	**1h**, *p*-FC_6H_4	**2a**, Ph	84	82/18	93
8	**1i**, *p*-ClC_6H_4	**2a**, Ph	55 (90[e])	83/17	92
9	**1j**, *p*-BrC_6H_4	**2a**, Ph	50 (92[e])	88/12	96
10	**1b**, Ph	**2b**, *p*-MeC_6H_4	51	87/13	92
11	**1b**, Ph	**2c**, *p*-$MeOC_6H_4$	74	76/24	92
12	**1b**, Ph	**2d**, *p*-FC_6H_4	62	93/7	92
13	**1b**, Ph	**2e**, *p*-ClC_6H_4	72	83/17	91
14	**1b**, Ph	**2f**, *p*-$NO_2C_6H_4$	nr	—	—

[a] Molar ratio: **2**/**1**/Cs_2CO_3/$[PdC_3H_5Cl]_2$/**L3** = 3/1/3/0.02/0.04.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Determined by HPLC.
[e] Yield based on the recovery of **1**.

the products in high yield by elevating reaction temperature to room temperature, with moderate enantioselectivity and low regioselectivity (Eq. 3). For secondary and tertiary aliphatic alcohols, there was no reaction even at room temperature.

The absolute configuration of product **3b** was determined as (*R*) by comparing the sign of specific rotation of **3b** with that of known compound reported in the literature.[4b]

3. Conclusion

In summary, we have succeeded in the Pd-catalyzed regio- and enantio-selective allylic substitution reaction with substituted benzyl alcohols, affording the corresponding products in high regioselectivity and enantioselectivity. The extension of the substrate scope and the applications of the products in organic synthesis are under way.

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9. *Typical experimental procedure*: To a flame-dried Schlenk tube were added $[Pd(C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol), (*S*, R_{phos}, *S*)-**L3** (6.7 mg, 0.010 mmol), toluene (1.0 mL) with stirring for 30 min, and then allyl substrates **1b** (58.5 mg, 0.25 mmol), Cs_2CO_3 (244.0 mg, 0.75 mmol), benzyl alcohols **2a** (81.2 mg, 0.75 mmol), and toluene (2.0 mL) were added subsequently. The resulting mixture was stirred at −5 °C for 40 h (TLC control). The reaction mixture was filtrated with silica gel and washed with CH_2Cl_2. The solvent was removed in vacuo. The regioselectivity was determined by ^1H NMR of the crude residue. The crude residue was purified by flash column chromatography using mixtures of ethyl acetate/petroleum ether as the eluent affording the product **3** (45.9 mg, 82% yield).
Compound **3**: $[\alpha]_D^{20} = +15.0$ (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (major isomer): 7.41–7.23 (m, 10H), 6.06–5.94 (m, 1H), 5.34–5.22 (m, 2H), 4.85 (d, *J* = 6.3 Hz, 1H), 4.54 (s, 2H); δ (minor isomer): 6.64 (d, *J* = 15.9 Hz, 1H), 6.38–6.28 (m, 1H). HPLC: Chiralcel OJ–H, hexane/^{i}PrOH = 98/2, flow rate = 0.7 mL/min, λ = 214 nm, t_R = 19.0 min (minor), 23.9 min (major).